

C1  
Cmt

unsaturated, a dicarbonate diradical of the formula  $-C(O)-O-(CH_2)_d-O-C(O)-$  where d is an integer from 2-10, and an oligomeric diradical represented by the formulas  $-R-C(O)-$ ,  $-R-C(O)-(CH_2)_c-C(O)-$ , or  $-R-C(O)-O-(CH_2)_d-O-C(O)-$  where c is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone;

wherein -G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, [or] and tresyl;

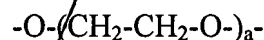
wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.

17. (Amended) A method of making a tissue adhesive consisting of the step of forming a mixture of

- Jan 23
- i) a first aqueous mixture of about 20-60 wt/vol % serum albumin in about 0.01-0.25 molar buffer at a pH in a range of about 8.0-11.0,
- ii) a second aqueous mixture of about 50-800 mg/ml of a crosslinking agent having a molecular weight in a range of about 1,000-15,000, wherein the crosslinking agent is of the formula
- C2



wherein -PEG- is a diradical fragment represented by the formula



wherein a is an integer from 20-300;

wherein -LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula  $[-C(O)-]$ , a monoester diradical of the formula  $[-(CH_2)_bC(O)-]$  where b is an integer from 1-5, a diester diradical of the formula  $[-C(O)-(CH_2)_c-C(O)-]$  where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, a dicarbonate diradical of the formula  $-C(O)-O-(CH_2)_d-O-C(O)-$  where d is an integer from 2-10, and an oligomeric diradical represented by the formulas  $-R-C(O)-$ ,  $-R-C(O)-(CH_2)_c-C(O)-$ , or  $-R-C(O)-O-(CH_2)_d-O-C(O)-$  where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the

group consisting of lactide, glycolide, trimethylene carbonate, caprolactone and p-dioxanone;  
and

wherein -G is a leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, [or] and tresyl; and

wherein a combination of the first and second mixtures is initially liquid and then cures on the surface of tissue to give a flexible, substantive matrix which bonds to the tissue and has a burst strength greater than about 10 mmHg.

180. The method of claim 179 wherein the crosslinking agent is of the formula  
G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-(CH<sub>2</sub>-CH<sub>2</sub>-O)-<sub>a</sub>-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH<sub>2</sub>)<sub>b</sub>C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula -C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)-, or -R-C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

206.61 The method of claim 205 wherein the matrix has a burst pressure of about 90 mmHg or greater.

212. The method of claim 211 wherein the crosslinking agent is of the formula  
G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-(CH<sub>2</sub>-CH<sub>2</sub>-O)-<sub>a</sub>-

where a is an integer from 20-300;

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conclude

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula  $-C(O)-$ , a monoester diradical of the formula  $-(CH_2)_bC(O)-$  where b is an integer from 1-5, a diester diradical of the formula  $-C(O)-(CH_2)_c-C(O)-$  where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula  $-C(O)-O-(CH_2)_d-O-C(O)-$  where d is an integer from 2-10, or an oligomeric diradical represented by the formulas  $-R-C(O)-$ ,  $-R-C(O)-(CH_2)_c-C(O)-$ , or  $-R-C(O)-O-(CH_2)_d-O-C(O)-$  where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

242. The method of claim 241 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

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-PEG- is a diradical fragment represented by the formula

$-O-(CH_2-CH_2-O)_a-$

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula  $-C(O)-$ , a monoester diradical of the formula  $-(CH_2)_bC(O)-$  where b is an integer from 1-5, a diester diradical of the formula  $-C(O)-(CH_2)_c-C(O)-$  where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula  $-C(O)-O-(CH_2)_d-O-C(O)-$  where d is an integer from 2-10, or an oligomeric diradical represented by the formulas  $-R-C(O)-$ ,  $-R-C(O)-(CH_2)_c-C(O)-$ , or  $-R-C(O)-O-(CH_2)_d-O-C(O)-$  where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

275. The method of claim 274 wherein the crosslinking agent is of the formula

G-LM-PEG-LM-G

wherein:

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-PEG- is a diradical fragment represented by the formula

*C7 conclude*  
-O-(CH<sub>2</sub>-CH<sub>2</sub>-O-)<sub>a</sub>-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH<sub>2</sub>)<sub>b</sub>C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula -C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)-, or -R-C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

*C8*  
318. The method of claim 317 wherein the crosslinking agent is of the formula G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-(CH<sub>2</sub>-CH<sub>2</sub>-O-)<sub>a</sub>-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH<sub>2</sub>)<sub>b</sub>C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula -C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)-, or -R-C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

*C9*  
351. The method of claim 350 wherein the crosslinking agent is of the formula G-LM-PEG-LM-G

wherein:

*ag conclude*

-PEG- is a diradical fragment represented by the formula

-O-(CH<sub>2</sub>-CH<sub>2</sub>-O)-<sub>a</sub>-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH<sub>2</sub>)<sub>b</sub>C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula -C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)-, or -R-C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

*CH*

382. The method of claim 381 wherein the crosslinking agent is of the formula  
G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-(CH<sub>2</sub>-CH<sub>2</sub>-O)-<sub>a</sub>-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH<sub>2</sub>)<sub>b</sub>C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula -C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)-, or -R-C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

*CH*

416. The method of claim 415 wherein the crosslinking agent is of the formula  
G-LM-PEG-LM-G

wherein:

-PEG- is a diradical fragment represented by the formula

-O-(CH<sub>2</sub>-CH<sub>2</sub>-O)-<sub>a</sub>-

where a is an integer from 20-300;

-LM- is a diradical fragment selected from the group consisting of a carbonate diradical of the formula -C(O)-, a monoester diradical of the formula -(CH<sub>2</sub>)<sub>b</sub>C(O)- where b is an integer from 1-5, a diester diradical of the formula -C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)- where c is an integer from 2-10 and where the aliphatic portion of the diradical may be saturated or unsaturated, and a dicarbonate diradical of the formula -C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where d is an integer from 2-10, or an oligomeric diradical represented by the formulas -R-C(O)-, -R-C(O)-(CH<sub>2</sub>)<sub>c</sub>-C(O)-, or -R-C(O)-O-(CH<sub>2</sub>)<sub>d</sub>-O-C(O)- where c is an integer from 2-10, d is an integer from 2-10, and R is a polymer or copolymer having 1-10 monomeric fragments selected from the group consisting of lactide, glycolide, trimethylene carbonate, caprolactone, and p-dioxanone; and

-G is the leaving group selected from the group consisting of succinimidyl, maleimidyl, phthalimidyl, imidazolyl, nitrophenyl, and tresyl.

#### REMARKS

In the action mailed June 20, 2000, at paragraph 2, the examiner noted that applicants had not responded to the requirement set forth in paragraph 4 of the final office action. In paragraph 4 of the final office action, the examiner pointed out several amendments to claims 1 and 17 that did not comply with 37 C.F.R. 1.121(b).

Applicants have presented claims 1 and 17 above, as amended in compliance with section 1.121(b). Applicants have also corrected the typographical errors that were present in the amendment filed September 30, 1999.

For example, the examiner noted that in the last line of claim 1, "than" was changed to "then," and this change was not marked in compliance with section 1.121(b). In fact, this was a typographical error; applicants did not intend the claim to read "then." The correct wording is reflected in claim 1, above. Similarly, in claim 17, at page 4 of the amendment, the word "radical" appeared. This was not meant as an amendment, but was instead a typographical error. The claim should have read "diradical," and this correction has been made in claim 17, above.

The examiner also pointed out that a comma was simply omitted from claim 17 after the word "formula," instead of appearing in brackets. This omission has been corrected in claim 17, above. A similar omission has also been corrected in claim 1. Applicants apologize for any confusion caused by these errors.